Interventions for Changing Brain Function in Clinical Disorders

Meng Yuan [1], Qingjun Zhu [2]

[1] University of California San Diego, San Diego, 92093, USA

[2] Fudan Development Institute, Fudan University, Shanghai, China

Meng Yuan and Qingjun Zhu are Co-First Author

Abstract. Historically, restoring brain function after injury or disease has been extremely difficult. However, over the past few decades, new techniques have emerged for reversing or postponing the deficits in behavior that accompany such injury. This paper reviews several current interventions for improving brain function in clinical settings: deep-brain stimulation, transcranial magnetic stimulation, physical exercise, and cognitive training. These interventions have been used in a wide range of clinical disorders, including Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, depression, stroke, and various psychiatric conditions. Findings suggest that these clinical interventions are associated with relatively modest improvements in outcome and should not be considered first-line treatments for most disorders. However, ongoing research continues to refine these techniques to establish more reliable neural pathways for improving clinical outcomes; to more precisely understand the neural mechanisms underlying various disorders; and to improve the delivery of the interventions.

Keywords: Clinical Disorders; Transcranial Magnetic Stimulation; Neural Pathways; Improving Clinical Outcomes

1. Introduction

As the most complex part of the human body, the brain plays the significant role in controlling emotion, sensory information, motor skills, breathing, temperature, vision, etc. However, the brain is also fragile that injuries of the brain will cause various kinds of diseases. Brain disorders pose a significant disease burden globally. In particular, western societies are currently confronted by a growing elderly population, which is accompanied by the increased incidence of such diseases (Joubert & Chainay, 2018). According to the WHO data that even in 2007, brain diseases affected 1 in 6 people worldwide. Distinct categories of brain diseases will impact different functions. Commonly, brain diseases include neurodegenerative diseases such as Huntington's disease, Parkinson's Disease, Trauma, dementia like Alzheimer's disease, and common mental disorders/illness such as depression, anxiety, schizophrenia, etc. Although the morbidity of brain diseases is high, they can be alleviated to some extent. This phenomenon is attributed to neuroplasticity, the ability to alter the brain's activity by reorganizing its structure, function, or connections in response to intrinsic or extrinsic stimuli. (Berlucchi, G., & Buchtel, H. A.,2009)

Imbalance of neurontransmitters in people's brain will cause thse diseases. To control brain diseases, there are many treatments that have been applied. Medication is the primary and wide treatment of brain disorders by directly improving the brain's abnormality since it's considered as a supplement/weakening to the unnormal chemical to balance patients'brains. For patients who get Alzheimer's disease, acetylcholine is usually lacked, and this will also impact other nerves that rely on acetylcholine to send information. Although neurodegenerative diseases are irreversible, corresponding medication can help increase the concentration of acetylcholine in patients brain and encourage communication between nerve cells, so that help slow or manage memory loss, thinking and reasoning difficulties, as well as day to day functioning. (Bartus, R. T. et al., 1982) Chemical imbalances will also lead to mental disorders. Anxiolytics, antipsychotics and antidepressants, and mood stabilizers are commonly used for treating mental disorders. However, Medication still has limitations that long-term use may cause resistance. Howes, O. D., Thase, M. E., & Pillinger, T. (2022). found that almost 20-60% patients with mental disorders suffered from drug treatment

resistance. In particular, poor understanding of neurobiology, heterogeneity and absence of consensus criteria can reinforce treatment resistance. Similarly, people who suffer from Parkinson's disease usually rely on the drug named levodopa, but in some cases, patients will fail to respond altogether. (Beckers, M., Bloem, B.R. & Verbeek, M.M.,2022) Therefore, there're still some limitations on the application of medications.

Besides medication, psychotherapy is another common treatment to change brain and explains neuroplasticity. In particular, systematic studies suggest that patients with major depressive disorder (MDD), obsessive-compulsive disorder, social anxiety disorder, posttraumatic stress disorder, etc., may experience changes in brain function as a result of cognitive-behavioral therapy (CBT), dialectic behavior therapy (DBT), psychodynamic psychotherapy, and interpersonal psychotherapy (BPD). (Brody AL et al., 2001; Goldapple K et al.,2004; Baxter LR Jr, et al.,1992; Straube T, et al.,2006; Felmingham K, Kemp A, Williams L, et al.,2006) To illustrate, according to Lehto SM et al.,2008, 19 depressive outpatients got 12-months of psychodynamic psychotherapy in the study. Eight of the individuals were diagnosed with atypical depression. SPECT brain imaging with the [123I] nor-Î2-CIT radioligand was used to measure the density of the midbrain serotonin transporter and the striatum dopamine transporter before and after psychotherapy. Researchers found that, in contrast to patients with standard depression, patients with atypical depression experienced a significant increase in midbrain serotonin transporter density during psychotherapy. Even if they are still in the early stages, research employing neuroimaging to assess the effects of psychotherapy will eventually help us better understand how various psychotherapies operate. Future studies of the efficiency of psychotherapy, when considered about neuroplasticity, should be continued to improve.

Since the popularity of brain disorders has become more widespread these years, it's significant for people, especially those who are not majoring in neuroscience/psychology majors to understand how other treatments methods, including advanced technology like Deep Brain Stimulation and Transcranial magnetic stimulation that can chang patients' brain, thereby to achieve therapeutic goals. Therefore, this article aims to provide detailed and clear information of other techniques based on neuroplasticity.

2. Deep Brain Stimulation

One of the most significant developments in neuroscientific medicine is deep brain stimulation (DBS), a surgical procedure used to treat neurological disorders using an electrical current applied to the brain. DBS involves injecting electrodes into the frontal cortex, and electrical impulses produce these sensors to control irregular impulses. The treatment procedure involves attaching wires to a minute device fitted beneath the skin near the collarbone. A microchip device is positioned beneath the skin in a person's upper chest to regulate the depth of sensory input during deep brain stimulation. Deep brain stimulation can be used to treat musculoskeletal conditions such essential tremors, Parkinson's disease (PD), dystonia, and mental problems. Only those whose symptoms are not under control with therapy are eligible for this surgery. As of 2019, experts estimate that since the 1980s, about 160,000 patients have received treatment to implant a DBS device. (Lozano, A. M., & Lipsman, N, 2013) DBS facilitates detecting and repairing abnormal neural signatures in the brain, promotes technical advancement, and improves therapeutic results. (Kühn, A. A et al., 2008)

DBS has increasingly become an effective therapy option for PD, a progressive neurodegenerative disorder marked by the loss of neuronal dopamine production in the brain. Movement-related symptoms of Parkinson's disease such as as tremors, stiffness and slowness are caused by disorganized electrical signals. (Schuepbach, W. M. et al.,2013) The introduction of DBS enabled the interruption of irregular signals which would cause tremors or other movement symptoms.

The effectiveness of DBS in treating PD has been demonstrated in various experiments. For example, Perestelo-Perez et al., 2014 found that DBS was superior to BMT with regard to enhancing motor control and medication doses in PD patients. Moreover, experiments conducted by De long and Benabid have demonstrated the effectiveness of DBS in the treatment of PD. Specifically, their

research focused on understanding the role of the basal ganglia in movement, in ascertaining the neurophysiology of PD. Clinical trials have also shown that DBS provides better results than the best medical therapy for PD. In another experiment, Weaver et al. compared long-term outcomes of DBS of globus pallidus intern (GPi) and subthalamic nucleus (STN) for patients with PD. The results showed an improvement in motor function and health-related quality of life. Overall, past experiments have demonstrated the effectiveness of DBS in treating PD.

Besides Parkinson's disease, deep brain stimulation may be used to treat Alzheimer's disease. Alzheimer's is a chronic degenerative disease related to amnesic dementia. It is the most common cause of dementia. During treatment, DBS is used to stimulate basal nuclei of Meynert and the frontal lobe. As a result, the patient experiences improved memory, language fluency, semantics, and numerical ability. (Aldehri M et al., 2018) Another brain disorder that could be treated with DBS is drug-resistant refractory epilepsy. Epilepsy is a chronic brain disease marked by two or more gratuitous seizures. Refractory epilepsy refers to a situation where a patient has used at least two anticonvulsants with no improvement. The treatment involves stimulation of central-medial and anterior nuclei of the thalamus. The treatment makes the patient antiepileptogenic. (Zangiabadi, N et al., 2019)

Drug-resistant obsessive-compulsive disorder (OCD) could also be treated through deep brain stimulation. OCD is a neurological disorder marked by obsessions in the form of recurrent thoughts. The treatment involves the stimulation of the internal capsule, ventral striatum, ventral capsule, inferior thalamic peduncle, and subthalamic nucleus (Marin et al., 2022). The treatment leads to symptom improvement. Drug-resistant Gilles Tourette syndrome can also be treated through DBS. The condition is marked by repetitive, involuntary, and stereotyped movements accompanied by tics. The treatment procedure stimulates the internal pale globe. Lastly, DBS could be used to treat drug-resistant depression. Depression is a mental disorder marked by feelings of sadness, tiredness, and loss of interest, among others. Depression is declared to be drug-resistant when a patient has used two or more antidepressants without any improvement. DBS treatment stimulates subcallosal cingulate leading to solid and sustained antidepressant response.

What's more, experimental deep brain stimulation in animal models is conducted to assess new indications and novel technology. In electrophysiological studies, scientists found typical alterations at various anatomic locations that demonstrated changes at the target location and distal tissues. DBS is a viable therapeutic approach for depression that is unresponsive to therapy. Its effectiveness has been evaluated in animal research using a variety of results. (Al-Harbi K. S., 2012) According to the analysis, physiological and electrophysiological indicators have the most promise for stress.

In one of the experiments, DBS was performed in freely moving rats. Validation studies were conducted in two animal models. One was a rat with PD and the other was a rat with Huntington's disease. The impact of deep brain stimulation was assessed in varying behavioral tasks measuring motor and cognitive functions. The findings of the experiment showed that deep brain stimulation of the subthalamic nucleus can enhance parkinsonian motor disability. However, it can also cause behavioral side effects similar to the clinical situation. Further, the experiment showed that deep brain stimulation of the globus pallidus can enhance motor and cognitive symptoms in a rat model of Huntington's disease.

In another experiment involving animals, the researchers sought to understand how subthalamic nucleus deep brain stimulation relieves numerous motor symptoms of Parkinson's disease. The experiment used electrical artifact-free GCaMP fiber photometry to examine activity in basal ganglia nuclei during subthalamic nucleus deep brain stimulation in parkinsonian mice (Schor et al.). The results established that subthalamic nucleus deep brain stimulation's therapeutic effect is achieved through interruption of movement-linked STN activity, rather than inhibition or antidromic activation. The findings offer insights into optimizing Parkinson's disease treatment.

Another experiment where DBS was applied to animals aimed to explore the effects of NAcore and NAshell DBS on aspects of heroin taking and seeking. The experiment used rats. NAcore and NAshell DBS were administered following a preset schedule to two groups of rats (Schippers et al.)

The results showed that NAcore and NAshell DBS did not change heroin self-administration. However, it decreased cue. Overall, the experiment showed that NAcore DBS reduces motivation for heroin-taking and cue-conditioned behaviors.

However, the current limitations of DBS still exist. The insertion of the stimulator has a negligible possibility of causing brain hemorrhage or infection. Headaches, tremors, edem of the brain tissue, and short-term discomfort following surgery are possible complications. Although less traumatic, the such operation only requires minor surgical intervention but carries considerable risk.

3. Transcranial Magnetic Stimulation

Transcranial magnetic stimulation is a safe, non-invasive technique used in many areas of neurophysiological research. The pulses delivered by the wires over the scalp change the magnetic field, which can elicit potential change among the neurons in the cortical region of interest therefore changing the activity of neurons. Even though the mechanism behind how TMS alters neural connections remains largely unknown, it allows researchers to utilize its characteristics and develop new applications in many settings. As new technologies and methods develop, newer forms of TMS are introduced to the field of neuroscience, including repetitive transcranial magnetic stimulation (rTMS), deep transcranial magnetic stimulation (dTMS) (Roth et al., 2002), and theta burst stimulation (TBS) (Huang et al., 2007). Depending on the frequency delivered to the cortex, the simulation can either have excitatory effect (fast rTMS = 10 - 30 Hz) or inhibitory effect (slow rTMS = 1 Hz). One utilization of TMS is the ability to create temporary lesions at the desired cortical areas, and by combining with the observed behavioral changes, this allows researchers to establish causal relationships of a specific brain area and its function. Being able to change the potentials of neurons gives researchers an insight into its function to manipulate neural connections and examine certain brain circuits. Cash et.al (2021) developed an effective method for establishing a personalized stimulation site that maximizes the treatment outcome of rTMS for resistant depression by targeting individualized brain connection of the subgenual cingulate cortex (SGC) network and the effect is shown to maintain over time. Various types of TMS as a treatment tool in therapies are shown to have promising effects in treating neuropsychological disorders such as medication-resistant depression (Hoy & Fitzgerald, 2014), improving language cognitive response in chronic Schizophrenia patients (Shishkovskaia et al., 2022), and generalized anxiety disorder. (Diefenbach et al., 2015) TMS is also applied widely in physical rehabilitation, motor function improved more when TMS as an adjuvant is paired with motor training compared to solely doing the motor training. (Narayana et al., 2014) The increased motor performance suggests the connectivity-enhancing effect of TMS and it further raises the question regarding TMS-induced synaptic plasticity. As previously talked about, TMS can induce changes in neuron communication, which is a dominant part of forming neural plasticity, then it is possible to consider applying TMS to augment certain neural connectivity for the purpose of regaining functions once lost due to traumatic events.

Several studies have shown promising results regarding enhanced neural connections by stimulating neural circuits. Jackson et al. (2006) demonstrated the increased synaptic connections between two sites of the motor cortex by using paired stimulation in primates. A stable reorganization of the visual cortex responsible for orientation was observed in cats, the mice in the experimental group underwent a single orientation exposure training after applying 10 Hz rTMS to the primary visual cortex, and the result showed the area which represents the stimulus orientation enlarged in the orientation map. The diminished activation of the area that represents orientation preference was observed after the 10 Hz rTMS session compared to pre-rTMS images, and this reduction was not seen in the 1 Hz condition and the sham condition. The result provides new insight into a possible mechanism behind TMS-induced plasticity, in which rTMS was able to introduce neurons into a stage that interrupts previous connections and increases the sensitivity to allow new pathways to establish. (Kozyrev et al., 2018) Further studies can build on these results by trying to establish a causal relationship between the cortical changes and behavioral changes. TMS as a non-invasive approach

to stimulate neural connections is often used to better understand this effect in humans. Stimulation between the ventral premotor cortex (PMv) and the primary motor cortex (M1) pathway continues to elevate manual performance after 30 minutes post-stimulation. (Fiori et al., 2018) Fifty-four healthy participants were recruited and randomly assigned into three groups, the experimental group received stimulation in the direction of PMv to M1, the active control group received a reversal of direction and a sham group. Two sets of visuomotor behavioral tasks were administered to the participants at baseline, pre-stimulation, immediately after stimulation, and 30 minutes post-stimulation. The result showed persistent enhanced performance of the visuomotor tasks in the experimental group compared to the other two groups, as an indication of the reorganization effect of TMS and the need to consider the direction of the current delivered in addition to the location. Though there is abundant evidence that TMS not only alters the excitability of neurons, but also makes reorganizing neural networks between areas possible, and using TMS as an alternative treatment option for medication-resistant depression has been approved by the FDA, the application of TMS in the clinical setting for motor rehabilitation requires further investigation and clinicians still hold conservation regarding this method.

TMS-induced plasticity is widely studied for the purpose of regaining functions in post-stroke patients. Two most common focuses within this area are prognosis and treatment after stroke. Being able to accurately assess the maximum possible recovery is necessary for designing the treatment plan and setting clearer cut-off points for stratification in research. Stinear et al. (2012) developed a new algorithm called PREP to assess the possible recovery of the upper limbs, by using TMS to check the presence of motor-evoked potentials (MEP). The ability to successfully elicit an MEP is a big determinant of the possibility to regain upper limb functions. The team used diffusion-weighted magnetic resonance to confirm the integrity of the MEP pathway found by TMS stimulation, and most predictions of motor outcomes at 12 weeks were confirmed. Though the group achieved high positive and negative predictive values (>80%), and high specificity and sensitivity (>70%) with this new algorithm, individual variability in response to the TMS is still an important factor to consider therefore prognosis cannot be solely based on the TMS result, and future research can address this issue by discovering more reliable pathways or new methods to deliver the stimulation.

A recent study demonstrated a new possible way to apply TMS in treatment, Buetefisch et al. (2022) illustrated a neuroprotective mechanism of low-frequency rTMS in post-ischemic stroke rats. Rats who received low-frequency rTMS within 3 hours post the onset of stroke displayed a significant reduction in cell death and infarct volume, and better sensorimotor function performance than the control group 3 - 21 days after receiving the stimulation. Another case study reported a patient with global aphasia due to a stroke, who received a 10-day continuous theta burst stimulation treatment post-stroke over the right pars triangularis. The language ability and life quality were measured before, 1 day, 2 months, and 12 months after the treatment. The study found the most significant speech and language comprehension improvements happen at one-day post-treatment and moderate improvement in reading in later follow-up measures. (Georgiou et al., 2020) This is a case study of one individual, and it's necessary to consider individual variability, and further research could consider using a bigger sample size and more precise stratification to identify the class of patients who can benefit from this treatment approach. TMS as a treatment option has huge potential to be applied in the clinical field for stroke recovery, but individual responses to the stimulation make the technique selectively effective to specific patients, so it's important to discover the reasons for this individual variability, two aspects to consider include genetics and locations of the lesion. This method is still under investigation that requires more longitudinal studies and bigger samples to contemplate the individual variability of the outcome and the time period in which the effect could last. And future studies can divide participants into groups based on the different timing they receive treatment after the stroke to address a potentially critical period that results in the maximum possible recovery.

4. Physical Activity

A lifestyle that includes routine physical activities has been well-acknowledged to be beneficial in multiple aspects of both physical and mental health and increases lifespan among all age groups. Several animal studies have observed structural changes in the brain after physical training. Rats that have voluntary access to running wheels for six weeks show altered gene transcription in the mesolimbic neurocircuitry, a pathway known to be highly involved in reward mechanisms. (Greenwood et al., 2010) Another study received a similar result that exercise remodels the gene which contains neurotrophic factors that are necessary for regulating hippocampal learning in rats. (Gomez-Pinilla et al., 2011) By measuring the change of several types of protein in a rat's hippocampal area after physical exercises, researchers found an up-regulation in proteins that are involved in cognitive function, a possible mechanism behind the structural changes as the result of exposure to long-term exercise. (Ding et al., 2006) Animal studies have demonstrated physiological changes in the brain caused by physical activities and provided some explanations about this process. Researchers further confirmed the observation can also be found in humans. At the cellular level, Maddock et al. (2016) were interested in the product of the increased neural metabolism during physical activities, the group compared the neurotransmitter levels of the recruited volunteers before and after the physical activity measured by proton magnetic resonance spectroscopy, and the immediate result showed a significant increase in glutamate and GABA level in the visual cortex, and a positive correlation was found between the resting glutamate level and the exercise level of the participant in the past week. The results suggest immediate observable metabolic changes in the brain are happening during exercise and this process is a possible substrate for further more complex network plasticity to build on. Long-term physical activity alters the frontal-subcortical connectivity in older age adults. (Dorsman et al., 2020) The functional connectivity (FC) was measured by task-free functional MRI and compared with default FC, and the result was analyzed with the self-reported exercise level in the past week. Within-subject increase in the activity level is observed with greater frontal-subcortical FC but not in other well-studied pathways, suggesting physical activity does induce changes at a network level, and the effect could be region specific. Different types of training can elicit plasticity in a specific pathway, instead of aerobic exercises, Rogge et al. (2018) tested if balance training can also make structural differences in the brain. They randomly assigned the 37 healthy adult participants to either balance training or relaxation training group, and the frequency of training was twice a week for a duration of 12 weeks. Structural MRI scans and balance assessment were acquired before and after the entire training, and the results showed improved balance performance in the balance training group compared to the relaxation group, and cortical thickness increased in several visual and regions that involve self-motion perception, also a reduction in the putamen volume. Another research also found an increase in several regions of the brain and the total volume in children who received radiation treatment for a brain tumor, and better behavioral outcomes than the control group who have the same condition but receive no exercise training. (Szulc-Lerch et al., 2018) Their research demonstrated the effect of exercise could induce both structural and functional changes, and as previously mentioned, the altered brain chemicals might be one possible mechanism behind this increase in grey matter, and since there is limited human research on this topic, so further studies can explore other explanations by more frequent measuring within the period of training regarding the changes at both cellular and structural level to see if a similar cellular activity can be found in humans.

Since several studies have shown changes in the physical structure of the brain and behavioral improvements due to physical exercise, the next step would be to consider the utilization of this property. Physical activity could be seen as a nonpharmaceutical, noninvasive, low-cost preventative approach to multiple disorders that involve cognitive degradation and promote cognitive health in those patients. Not only regular exercise in elderlies is associated with a lower risk of Alzheimer's disease (AD), (Santos-Lozano et al., 2016) patients with Alzheimer's disease who actively participated in physical activity show larger prefrontal and hippocampal areas, (Erickson et al., 2012) and in genetically determined autosomal dominant Alzheimer's patients, the observed AD-like

pathology is lower in participants who regularly engage in physical activities and better cognitive function. (Müller et al., 2018) Huntington's is a currently untreatable fatal disease in which people who carry the mutated gene will inevitably develop symptoms such as motor disability and cognitive decline. Pang et al.(2006) reared transgenic mice in 2 conditions: standard and running wheels provided, and the running wheel group showed delayed onset of the rear-paw clasping, an abnormal behavior that represents impaired motor coordination and spatial working memory, suggests the potential effect of voluntary physical activities to postpone the progression of symptoms. Not only neurodegenerative disease, but physical activities have also been shown to be helpful in other physical diseases that might cause significant cognitive distress. Type II diabetes can cause impaired cognition, especially in memory and executive function. A 12-week study has divided diabetic participants into 3 groups, three 40 minutes of walking training per week, 10000 steps daily monitored by a pedometer, or standard care. There are significant behavioral improvements in the 2 walking groups in both nonverbal and verbal memory, as well as cognitive attention. (Leischik et al.,2021) Another critical implication of their study is that high-intensity of physical activity is not required for improved cognition. Physical activity as an adjuvant to boost the outcome of cognitive behavioral therapies or medication treatment has produced promising results in multiple common psychiatric disorders and also provides a protective effect. To investigate the effect of physical exercise on depression-induced diseases such as increased metabolic syndrome that leads to a higher risk of developing cardiovascular diseases and diabetes, Kerling et al. (2015) recruited 42 inpatients with moderate to severe depressive disorder, all received psychotherapy and some combined with antidepressant medication treatment, 22 of them were assigned 3 physical activity sessions per week in addition to the usual care and the rest maintained the treatment as they previously received. The self-reported psychological symptoms and physiological measurement both improved significantly after six weeks of participation in the exercise group, suggesting additional physical activity to traditional treatments not only alleviates the symptoms of depression but also reduces the risk factors of developing depression-related physical diseases. Physicians always recommend physical activity in response to stress reduction, including in anxiety prevention and as a part of intervention. A study has shown improved working memory performance, reduced self-reported stress evaluation and salivary cortisol level after participating in instructed yoga practice for 8 weeks in older adults, indicating the enhanced function of the HPA axis on regulating stress response and the protective property of yoga against the cognitive decline due to aging. (Gothe et al., 2016) Apart from improved cognitive functions, physical health concerns among people with psychiatric disorders are exceedingly normal. For example, compare to the normal population, patient with schizophrenia spectrum disorder have 10-20 years shorter life expectancy due to multiple factors, and cardiovascular diseases is one of the most concerning ones and caused very high mortality. (Hennekens et al., 2005) Patients with severe psychological disorders are often reluctant to participate in voluntary physical activities, so it is necessary for healthcare providers to integrate an appropriate level of physical exercise into the traditional treatment plan depending on the individual.

Physical therapy is a part of the first-line treatment options to regain or improve motor performance in post-stroke and Parkinson's patients. It was observed that physical therapy such as task-oriented training can induce expanded hand representation in the motor cortex in infarcted monkeys which have local damage that impaired hand motor function, and improved motor performance, suggesting a causal relationship between cortical reorganization and task-oriented physical training. (Nudo et al., 1996) Once the motor-cortical changes induced by physical exercise are established, researchers started to consider establishing systematic treatment plans for disorders that involve motor impairments, and different approaches have been utilized to target specific concerns. Commonly seen physical therapies focus on balance, mobility, pain management, range of motion, grasp strength, and so on, and the outcomes are mostly positive. Long-term high-intensity exercise has been proven to improve both motor outcomes and emotional scores among mild to moderate stage Parkinson's patients. (Morberg et al., 2014) Nowadays, more and more focus on motor recovery has been combined with the use of modern technology, such as robot-assisted training for post-stoke patients

(Zhang et al., 2022), virtual reality-assisted therapy as an intervention for chronic stroke patients (Subramanian et al., 2013), and the use of mobile phone app directed training programs in Parkinson's disease. (Gao et al., 2021) Even though the result of some of the modern training methods doesn't show superiority over traditional methods, the involvement of new technologies might promote participation, and the investigation to find the proper way to utilize these tools still has great potential.

Physical activity is low-cost, promotes overall health, and there are many options for most people to easily participate in some kind of physical activity, but it also has some limitations when applied as a treatment option. First, physical activity by itself tends to have a small effect on relieving the symptoms, so physicians can't solely dependent on physical activity as the primary treatment. The subtle alleviation develops over a long period of time and the effect can't be seen immediately, so there's a higher chance of withdrawal. Second, it could not be applied to patients when there are physical comorbidities that limit participation in physical activities. Third, in the end stage of depression or other psychological disorders, the willingness to be active is very low. This situation is also seen in the end stage of other disorders that impair motor functions; the severity of the impairment has completely disabled the patient from producing any movements. So physical activity is an option for mild to the moderate stage in many disorders, but other forms of treatment should be considered for end stage patients.

Future research should establish clearer inclusion and exclusion criteria when recruiting participants. It's important to take medication and other forms of intervention into account when observing the effect of physical training. It would be better for the observed cortical changes in the brain could be accompanied by the improved behavioral outcome, so more meticulous design is necessary for developing powerful results. There's a need to develop individualized physical recovery plans to better accommodate different circumstances between patients and differentiate types of training based on patient profiles, meaning establishing more symptom-oriented methods. Also, as previously mentioned, more proper ways to involve modern technology in physical recovery should be investigated, and consider the cost-benefit when applying those methods.

5. Cognitive Training

As people age, changes in the brain negatively affect various aspects of cognition such as processing, working memory, and executive functions. Thus, addressing diseases caused by cognitive malfunction or decline in western societies is of utmost urgency. One of the popular therapies that have been advanced in addressing brain disorders is cognitive training. The latter involves structured and guided practice aimed at improving a given aspect of cognition such as memory (Irazoki et al., 2020). Cognitive training can be undertaken individually or in groups and has demonstrated effectiveness against brain disorders like dementia and schizophrenia (Guercio et al., 2019; Irazoki et al., 2020). Notably, the therapeutic value of cognitive training is based on neuroplasticity, which is the ability of the brain to make structural and functional changes in response to environmental stimuli.

Cognitive training is based on the assumption that cognition and/or the aging brain can be improved through various training exercises. The method often entails a series of repetitive laboratory or software-based exercises that focus on a specific element of cognition such as memory (Guercio et al., 2019). The tasks can be completed using a computer or paper and pen. At the behavioral level, cognitive training is expected to improve the performance of cognitive tasks and thus improve the independence of the elderly or other patients with brain disorders. At the brain level, cognitive training induces structural and functional changes such as cortical thickness and white matter integrity (Joubert & Chainay, 2018). Various technologies and training protocols have been developed for cognitive training for different brain disorders including dementia, traumatic brain disorders, and schizophrenia (Han, Chapman, & Krawczyk, 2018; Irazoki et al., 2020). In sum, cognitive training involves applying certain exercises to improve a specific element of cognition.

Several studies document evidence of successful uses of cognitive training in treating various brain disorders. Remarkably, a study by Liu et al. (2022) demonstrated that cognitive training could improve memory generalization in mice APP/PS1 mice. The study hinted at the potential effectiveness of cognitive training in treating Alzheimer's disease, whose etiology encompasses problems with memory generalization. Elsewhere, human studies have shown the effectiveness of cognitive training in treating schizophrenia (Guercio et al., 2019). The method works by stimulating the formation of more adaptive brain circuits. Equally, cognitive training has proved useful in reversing cognitive control impairments in patients with traumatic brain injury. In a study by Han et al. (2018), cognitive training-induced neuroplasticity in traumatic brain injury patients resulting in improved cognitive control compared to a control sample. Therefore, there is substantial evidence supporting the therapeutic utility of cognitive training in treating brain disorders.

Cognitive training methods assume neuroplasticity, i.e., the ability of the brain to change in structure and function due to environmental stimuli. In most studies of cognitive training, the mechanism of action often manifests in brain-level changes. For instance, in the study by Liu et al. (2022), functional magnetic resonance imaging (fMRI) revealed that cognitive training improved the functioning of the medial prefrontal cortex and the hippocampus. Thus, the observed improvement in memory generalization in the test mice was due to the functional improvements at the brain level. Other studies have also evidenced neuroplasticity as the mechanism through which cognitive training works. For instance, Park & Bischof (2022) observed that stroke patients, despite suffering significant brain damage, often show improvements with therapy. The improvements can only be explained in terms of neuroplasticity, which may encompass changes in neural activity or structure (Park & Bischof, 2022). Separately, the connection between neuroplasticity and cognitive training was demonstrated by Guercio et al. (2019) who found that the protocols of cognitive training can be more effective when paired with neuroplasticity enhancers. By improving neuroplasticity, cognitive training delivers more effective and lasting results. Neuroplasticity is therefore inseparable from cognitive training and acts as the method's underlying mechanism.

As a whole, cognitive training is an important therapy that can help to address brain disorders such as dementia, schizophrenia, and Alzheimer's disease, among others. The method works through a series of repetitive tests administered to patients to improve a specified cognitive function like memory. Cognitive training assumes neuroplasticity, without which the method cannot work. Its training exercises work by inducing structural and functional changes in the brain. Animal studies show changes in both structure and function at the brain level following the application of cognitive training methods. Other studies have suggested that cognitive training works better when combined with neuroplasticity enhancers. Consequently, neuroplasticity serves as the foundation upon which cognitive training interventions can be designed and improved.

6. Discussion

The application of these approaches tends to be more specific within certain populations, some methods show better effects in one disorder but may not cause any significant changes in others. The need to understand which method archives the maximum effect is important for designing treatment plans. Among several diseases that involve deteriorated cognitive functions, Alzheimer's disease, a neurodegenerative disease that affects the quality of life of over 6 million Americans, is one of the disorders that gained the most attention. DBS, physical activity, and cognitive training have yielded positive results on the improved cognitive abilities of Alzheimer's patients, and routine physical activity showed a lowered risk of developing Alzheimer's disease. At the end stage of Huntington's disease, both motor and cognitive functions will be impacted, and several studies used model animals of Huntington's disease showed DBS's effect from stimulating the globus pallidus, part of basal ganglia that's highly involved in motor control and is the region that is most affected in Huntington's patients, has produced improvement in the behavioral and motor tasks after the stimulation, and physical activity also showed delayed expression of symptoms. Normal aging has been linked with

brain atrophy that could result in deteriorated cognitive functions such as memory, multitasking, and processing speed. Training like physical activity and cognitive training appears to have an effect on maintaining above-average functioning abilities than populations without training. Several approaches have been applied in motor impairment disorders such as regaining post-stroke motor functions and Parkinson's disease. TMS has received the most attention when applied to post-stroke patients due to its applicable properties in motor ability diagnosis and treatment. Physical therapy is one of the most common treatment plans for post-stroke patients and Parkinson's patients for motor training, and cognitive training showed evidence of improved cognitive function that was damaged by the infarct. Several implantation locations for DBS have been proven to be effective in decreasing the presence of motor symptoms. It's also necessary to utilize neuroplasticity in psychiatric disorders to regain healthy brain activity or connections. Treatment of depression always prioritizes cognitive training such as cognitive behavioral talk therapy and medication. DBS and TMS can be considered when the previous two methods don't show alleviation of symptoms, and physical activity is always suggested to boost the treatment effect of depressive symptoms. Cognitive training has gained most positive outcomes besides medication in patients with Schizophrenia, and the involvement of other forms of approaches has gained attention and undergoing research. Each approach has its own limitations as well, since DBS needs to be surgically implanted, meaning the approach is invasive and has higher risks, so it's possible to cause serious complications, and people varies when determining the effective implantation locations. Several concerns regarding the application of TMS include individual variability, some people don't respond to the magnetic stimulation, or respond to stimulation to different pathways, and the response varies between individuals, so it's challenging to establish guidelines for standard care. Another research limitation on the capability of TMS in altering brain plasticity is that it could only reach the cortex, so it could not be applied to damage in the subcortical structures. Even though physical activity has low participation requirements, some populations are not suitable candidates for this type of recovery training, including limitations due to physical conditions and the drop-out rate is high. Cognitive training requires long-term participation and the effect tends to be minor and can't be directly measured.

Limitations. Currently, the mechanism of neuroplasticity still remains unclear and correct pathways haven't been well established for corresponding symptoms. Two people who show similar symptoms might have drastically different reasons or the mechanisms behind the occurrence of the symptoms and neurogenesis does not occur in most parts of the adult's brain, so it makes the repairment of neurological damages nearly impossible to happen and standardize. Even though the number of neurons in an adult's brain would not be easily changed, the connection between neurons can be altered through practice, exercise, or stimulation. It could be said that the brain is both easy and hard to be changed, because the formation is determined by countless factors during development but hard to be changed when the connection gets stable through repetitive enhancement. So, the goal of neuroplasticity is to set up reliable connections that correspond to a certain behavior or alter the connection of malfunctioned pathways.

Future directions. More and more advanced technologies could be used interdisciplinarity, so the combination of modern technology and neuroscience can yield very promising results. Neuroplasticity training that involves multiple sensory modalities has gained researchers' interest because some studies have shown that multiple types of sensory input can strengthen the result of some neuroplasticity training, and this property can later be used to maximize the recovery outcome of several motor disorders. Some aspect to consider within this field is the relationship between structural changes and behavior. It would be best if studies can show the conversion of altered structure to improved behavioral response, and apply multiple imaging methods to ensure the difference found between pre and post intervention. Taking the severity of symptoms into account when designing the experiment, it would be better to stratify patients into different severity groups when verifying the effect or design target treatment based on the severity. Future research can focus on utilizing neuroplasticity in early interventions such as function as a protective mechanism against

disorders. The exuberant neural connections may provide more functional reserve against certain disorders from developing or the early onset of symptoms.

References

[1] Joubert, C., & Chainay, H. (2018). Aging brain: the effect of combined cognitive and physical training on cognition as compared to cognitive and physical training alone - a systematic review. Clinical interventions in aging, 13, 1267–1301. https://doi.org/10.2147/CIA.S165399.

[2] World Health Organization. (2007, February 27). Neurological disorders affect millions globally: WHO report. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7555053/.

[3] Berlucchi, G., & Buchtel, H. A. (2009). Neuronal plasticity: historical roots and evolution of meaning. Experimental brain research, 192(3), 307–319. https://doi.org/10.1007/s00221-008-1611-6.

[4] Bartus, R. T., Dean, R. L., 3rd, Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. Science (New York, N.Y.), 217(4558), 408–414. https://doi. org/10. 1126/ science. 7046051.

[5] Howes, O. D., Thase, M. E., & Pillinger, T. (2022). Treatment resistance in psychiatry: state of the art and new directions. Molecular psychiatry, 27(1), 58–72. https://doi.org/10.1038/s41380-021-01200-3.

[6] Beckers, M., Bloem, B.R. & Verbeek, M.M. Mechanisms of peripheral levodopa resistance in Parkinson's disease. npj Parkinsons Dis. 8, 56 (2022). https://doi.org/10.1038/s41531-022-00321-y.

[7] Brody AL, Saxena S, Stoessel P, et al. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Arch Gen Psychiatry. 2001; 58: 631-640.

[8] Goldapple K, Segal Z, Garson C, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry. 2004; 61:34-41.

[9] Baxter LR Jr, Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry. 1992; 49:681-689.

[10] Straube T, Glauer M, Dilger S, et al. Effects of cognitive-behavioral therapy on brain activation in specific phobia. Neuroimage. 2006; 29:125-135.

[11] Felmingham K, Kemp A, Williams L, et al. Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress. Psychol Sci. 2007;18:127-129.

[12] Lehto SM, Tolmunen T, Joensuu M, et al. Changes in midbrain serotonin transporter availability in atypically depressed subjects after one year of psychotherapy. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:229-237.

[13] Lozano, A. M., & Lipsman, N. (2013). Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron, 77(3), 406–424. https://doi.org/10.1016/j.neuron.2013.01.020.

[14] Kühn, A. A., Kempf, F., Brücke, C., Gaynor Doyle, L., Martinez-Torres, I., Pogosyan, A., Trottenberg, T., Kupsch, A., Schneider, G. H., Hariz, M. I., Vandenberghe, W., Nuttin, B., & Brown, P. (2008). High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. The Journal of neuroscience: the official journal of the Society for Neuroscience, 28(24), 6165–6173. https://doi.org/ 10.1523/ JNEUROSCI. 0282-08.2008.

[15] Lozano, A. M., & Lipsman, N. (2013). Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron, 77(3), 406–424. https://doi.org/10.1016/j.neuron.2013.01.020.

[16] Kühn, A. A., Kempf, F., Brücke, C., Gaynor Doyle, L., Martinez-Torres, I., Pogosyan, A., Trottenberg, T., Kupsch, A., Schneider, G. H., Hariz, M. I., Vandenberghe, W., Nuttin, B., & Brown, P. (2008). High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. The Journal of neuroscience: the official journal of the Society for Neuroscience, 28(24), 6165–6173. https://doi.org/ 10.1523/ JNEUROSCI. 0282-08.2008.

[17] Schuepbach, W. M., Rau, J., Knudsen, K., Volkmann, J., Krack, P., Timmermann, L., Hälbig, T. D., Hesekamp, H., Navarro, S. M., Meier, N., Falk, D., Mehdorn, M., Paschen, S., Maarouf, M., Barbe, M. T., Fink, G. R., Kupsch, A., Gruber, D., Schneider, G. H., Seigneuret, E., … EARLYSTIM Study Group

(2013). Neurostimulation for Parkinson's disease with early motor complications. The New England journal of medicine, 368(7), 610–622. https://doi.org/10.1056/NEJMoa1205158.

[18] Perestelo-Pérez, L., Rivero-Santana, A., Pérez-Ramos, J., Serrano-Pérez, P., Panetta, J., & Hilarion, P. (2014). Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials. Journal of neurology, 261(11), 2051–2060. https://doi.org/10.1007/s00415-014-7254-6.

[19] Aldehri M, Temel Y, Alnaami I, Jahanshahi A, Hescham S. Deep brain stimulation for Alzheimer's Disease: An update. Surg Neurol Int. 2018 Mar 7; 9: 58. doi: 10.4103/sni.sni_342_17. PMID: 29576909; PMCID: PMC5858049.

[20] Zangiabadi, N., Ladino, L. D., Sina, F., Orozco-Hernández, J. P., Carter, A., & Téllez-Zenteno, J. F. (2019). Deep Brain Stimulation and Drug-Resistant Epilepsy: A Review of the Literature. Frontiers in neurology, 10, 601. https://doi.org/10.3389/fneur.2019.00601.

[21] Marin, G. et al. Deep Brain Stimulation in Neurological Diseases and Other Pathologies. Neurology Perspectives, vol. 2, 2022.

[22] Al-Harbi K. S. (2012). Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient preference and adherence, 6, 369–388. https://doi.org/10.2147/PPA.S29716.

[23] Buetefisch, C. M., Wei, L., Gu, X., Epstein, C. M., & Yu, S. P. (2022). Neuroprotection of Low Frequency Repetitive TMS after Ischemic Stroke in Rats. Annals of Neurology.

[24] Cash, R. F., Cocchi, L., Lv, J., Wu, Y., Fitzgerald, P. B., & Zalesky, A. (2021). Personalized connectivity-guided DLPFC-TMS for depression: Advancing computational feasibility, precision and reproducibility. Human brain mapping, 42(13), 4155-4172.

[25] Chung, S. W., Hoy, K. E., & Fitzgerald, P. B. (2015). Theta-burst stimulation: a new form of TMS treatment for depression?. Depression and anxiety, 32(3), 182-192.

[26] Diefenbach, G. J., & Goethe, J. W. (2015). Does TMS hold promise for generalized anxiety disorder. Psychiatr Times, 32(1), 26-26.

[27] Ding, Q., Vaynman, S., Souda, P., Whitelegge, J. P., & Gomez-Pinilla, F. (2006). Exercise affects energy metabolism and neural plasticity-related proteins in the hippocampus as revealed by proteomic analysis. European Journal of Neuroscience, 24(5), 1265-1276.

[28] Dorsman, K. A., Weiner-Light, S., Staffaroni, A. M., Brown, J. A., Wolf, A., Cobigo, Y., ... & Casaletto, K. B. (2020). Get moving! Increases in physical activity are associated with increasing functional connectivity trajectories in typically aging adults. Frontiers in aging neuroscience, 12, 104.

[29] Erickson, K. I., Weinstein, A. M., & Lopez, O. L. (2012). Physical activity, brain plasticity, and Alzheimer's disease. Archives of medical research, 43(8), 615-621.

[30] Gao, S., Kaudimba, K. K., Cai, J., Tong, Y., Tian, Q., Liu, P., ... & Wang, R. (2021). A mobile phone app-based Tai Chi training in Parkinson's disease: protocol for a randomized controlled study. Frontiers in neurology, 11, 615861.

[31] Georgiou, A. M., Phinikettos, I., Giasafaki, C., & Kambanaros, M. (2020). Can transcranial magnetic stimulation (TMS) facilitate language recovery in chronic global aphasia post-stroke? Evidence from a case study. Journal of Neurolinguistics, 55, 100907.

[32] Gomez-Pinilla, F., Zhuang, Y., Feng, J., Ying, Z., & Fan, G. (2011). Exercise impacts brain-derived neurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. European Journal of Neuroscience, 33(3), 383-390.

[33] Gothe, N. P., Keswani, R. K., & McAuley, E. (2016). Yoga practice improves executive function by attenuating stress levels. Biological psychology, 121, 109-116.

[34] Greenwood, B. N., Foley, T. E., Le, T. V., Strong, P. V., Loughridge, A. B., Day, H. E., & Fleshner, M. (2011). Long-term voluntary wheel running is rewarding and produces plasticity in the mesolimbic reward pathway. Behavioural brain research, 217(2), 354-362.

[35] Hennekens, C. H., Hennekens, A. R., Hollar, D., & Casey, D. E. (2005). Schizophrenia and increased risks of cardiovascular disease. American heart journal, 150(6), 1115-1121.

[36] Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. Neuron, 45(2), 201-206.

[37] Jackson, A., Mavoori, J., & Fetz, E. E. (2006). Long-term motor cortex plasticity induced by an electronic neural implant. Nature, 444(7115), 56-60.

[38] Kerling, A., Tegtbur, U., Gützlaff, E., Kück, M., Borchert, L., Ates, Z., ... & Kahl, K. G. (2015). Effects of adjunctive exercise on physiological and psychological parameters in depression: a randomized pilot trial. Journal of affective disorders, 177, 1-6.

[39] Kozyrev, V., Staadt, R., Eysel, U. T., & Jancke, D. (2018). TMS-induced neuronal plasticity enables targeted remodeling of visual cortical maps. Proceedings of the National Academy of Sciences, 115(25), 6476-6481.

[40] Kwon, Y. H., Son, S. M., Lee, J., Bai, D. S., & Jang, S. H. (2011). Combined study of transcranial magnetic stimulation and diffusion tensor tractography for prediction of motor outcome in patients with corona radiata infarct. Journal of rehabilitation medicine, 43(5), 430-434.

[41] Maddock, R. J., Casazza, G. A., Fernandez, D. H., & Maddock, M. I. (2016). Acute modulation of cortical glutamate and GABA content by physical activity. Journal of Neuroscience, 36(8), 2449-2457.

[42] Morberg, B. M., Jensen, J., Bode, M., & Wermuth, L. (2014). The impact of high intensity physical training on motor and non-motor symptoms in patients with Parkinson's disease (PIP): a preliminary study. NeuroRehabilitation, 35(2), 291-298.

[43] Müller, S., Preische, O., Sohrabi, H. R., Gräber, S., Jucker, M., Ringman, J. M., ... & Dominantly Inherited Alzheimer Network (DIAN). (2018). Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease. Alzheimer's & Dementia, 14(11), 1427-1437.

[44] Narayana, S., Zhang, W., Rogers, W., Strickland, C., Franklin, C., Lancaster, J. L., & Fox, P. T. (2014). Concurrent TMS to the primary motor cortex augments slow motor learning. Neuroimage, 85, 971-984.

[45] Nudo, R. J., Wise, B. M., SiFuentes, F., & Milliken, G. W. (1996). Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. Science, 272(5269), 1791-1794.

[46] Pang, T. Y. C., Stam, N. C., Nithianantharajah, J., Howard, M. L., & Hannan, A. J. (2006). Differential effects of voluntary physical exercise on behavioral and brain-derived neurotrophic factor expression deficits in Huntington's disease transgenic mice. Neuroscience, 141(2), 569-584.

[47] Rogge, A. K., Röder, B., Zech, A., & Hötting, K. (2018). Exercise-induced neuroplasticity: Balance training increases cortical thickness in visual and vestibular cortical regions. Neuroimage, 179, 471-479.

[48] Roth, Y., Zangen, A., & Hallett, M. (2002). A coil design for transcranial magnetic stimulation of deep brain regions. Journal of Clinical Neurophysiology, 19(4), 361-370.

[49] Santos-Lozano, A., Pareja-Galeano, H., Sanchis-Gomar, F., Quindós-Rubial, M., Fiuza-Luces, C., Cristi-Montero, C., ... & Lucia, A. (2016, August). Physical activity and Alzheimer disease: a protective association. In Mayo Clinic Proceedings (Vol. 91, No. 8, pp. 999-1020). Elsevier.

[50] Stinear, C. M., Barber, P. A., Petoe, M., Anwar, S., & Byblow, W. D. (2012). The PREP algorithm predicts potential for upper limb recovery after stroke. Brain, 135(8), 2527-2535.

[51] Subramanian, S. K., Lourenço, C. B., Chilingaryan, G., Sveistrup, H., & Levin, M. F. (2013). Arm motor recovery using a virtual reality intervention in chronic stroke: randomized control trial. Neurorehabilitation and neural repair, 27(1), 13-23.

[52] Szulc-Lerch, K. U., Timmons, B. W., Bouffet, E., Laughlin, S., de Medeiros, C. B., Skocic, J., ... & Mabbott, D. J. (2018). Repairing the brain with physical exercise: cortical thickness and brain volume increases in long-term pediatric brain tumor survivors in response to a structured exercise intervention. NeuroImage: Clinical, 18, 972-985.

[53] Terao, Y., & Ugawa, Y. (2002). Basic mechanisms of TMS. Journal of clinical neurophysiology, 19(4), 322-343.

[54] Zhang, L., Jia, G., Ma, J., Wang, S., & Cheng, L. (2022). Short and long-term effects of robot-assisted therapy on upper limb motor function and activity of daily living in patient's post-stroke: a meta-analysis of randomized controlled trials. Journal of NeuroEngineering and Rehabilitation, 19(1), 1-22.